

# Glycine Receptor

## Key References

Becker, L., et al., Disease-specific human glycine receptor  $\alpha 1$  subunit causes hyperekplexia phenotype and impaired glycine- and GABA(A)-receptor transmission in transgenic mice., *J. Neurosci.*, **22**, 2501-2512 (2002).

Grewer, C., Investigation of the  $\alpha 1$ -glycine receptor channel-opening kinetics in the submillisecond time domain., *Biophys. J.*, **77**, 727-738 (1999).

Harvey, R.J. and Betz, H., Structure, diversity, pharmacology and pathology of glycine receptor chloride channels., *In Handbook of Experimental Pharmacology*. (M. Endo, Y. Kurachi and M. Mishina, eds.) **147**, 479-497, Springer Press, Berlin-Heidelberg, New York, New York (2000).

Harvey, R.J., et al., GlyR  $\alpha 3$ : An essential target for spinal PGE<sub>2</sub>-mediated inflammatory pain sensitization., *Science*, **304**, 884 (2004).

Laube, B., et al., Modulation of glycine receptor function a novel approach for therapeutic intervention at inhibitory synapses?, *Trends Pharmacol. Sci.*, **23**, 519-527 (2002).

Lynch, J.W., Molecular structure and function of the glycine receptor chloride channel., *Physiol. Rev.*, **84**, 1051-1095 (2004).

Mascia, M.P., et al., Enhancement of homomeric glycine receptor function by long chain alcohols and anaesthetics., *Br. J. Pharmacol.*, **119**, 1331-1336 (1996).

Mihic, S.J., et al., Sites of alcohol and volatile anesthetic action on GABA<sub>A</sub> and glycine receptors., *Nature*, **389**, 385-389 (1997).

O'Shea, S.M., et al., Propofol restores the function of "hyperekplexic" mutant glycine receptors in *Xenopus* oocytes and mice., *J. Neurosci.*, **24**, 2322-2327 (2004).

Rees, M.I., et al., Hyperekplexia associated with compound heterozygote mutations in the beta-subunit of the human inhibitory glycine receptor (GLRB)., *Hum. Mol. Genet.*, **11**, 853-860 (2002).

Saitoh, T., et al., A novel antagonist, phenylbenzene  $\omega$ -phosphono- $\alpha$ -amino acid, for strychnine-sensitive glycine receptors in the rat spinal cord., *Br. J. Pharmacol.*, **113**, 165-170 (1994).

Schmieden, V., et al., Pharmacology of the inhibitory glycine receptor: Agonist and antagonist actions of amino acid compounds., *Mol. Pharmacol.*, **50**, 1200-1206 (1996).

## Overview

The amino acid glycine is a major inhibitory neurotransmitter in the vertebrate CNS. Glycinergic synapses are particularly abundant in spinal cord and brain stem, but are also found in higher brain regions including the hippocampus. The inhibitory actions of glycine are potently blocked by the alkaloid strychnine, a convulsant poison in man and animals. Strychnine poisoning causes disinhibition of motoneurons and leads to hyperexcitability, convulsions and death through respiratory failure. In addition, it produces strong pain syndromes and hyperacuity of visual and auditory responses via disinhibition of sensory processing areas, i.e. dorsal horn of the spinal cord, cochlear nucleus, inferior colliculus and retina.

In addition to its inhibitory postsynaptic action, glycine also acts as an excitatory transmitter. First, it serves as a co-agonist of the NMDA-subtype of excitatory glutamate receptors; second, glycine has been shown to have excitatory effects on embryonic neurons. Like postsynaptic inhibition, this excitatory response is blocked by strychnine and results from an altered chloride equilibrium potential at early stages of development.

The strychnine-sensitive, postsynaptic glycine receptor (GlyR) is a ligand-gated chloride channel protein that belongs to the nicotinic acetylcholine receptor family. Purification and molecular cloning has shown that in adult mammals the GlyR is a pentameric transmembrane protein composed of  $\alpha$  and  $\beta$  subunits. Pharmacologically distinct isoforms of the GlyR originate from the developmentally and regionally regulated expression of four distinct  $\alpha$  subunit genes ( $\alpha 1$ - $\alpha 4$ ).

GlyRs containing the  $\alpha 1$  subunit are highly expressed in adult spinal cord and brain stem, whereas  $\alpha 2$  GlyRs represent the major embryonically and early postnatally expressed GlyR isoform.  $\alpha 3$  GlyRs are highly concentrated in the dorsal horn of the spinal cord and have been shown to be the molecular substrate of prostaglandin E<sub>2</sub>-induced inflammatory pain sensitization. Expression of the GlyR  $\alpha 4$  gene has so far only been detected in non-mammalian vertebrates.

Expression of cloned GlyR  $\alpha$  subunits in *Xenopus* oocytes or mammalian cell lines creates glycine-gated strychnine-sensitive channels, which mimic GlyRs in primary spinal neurons in most of their pharmacological properties and may correspond to extrasynaptic receptors. Coexpression of the structural  $\beta$  subunit modifies the elementary conductance and channel blocker sensitivity of the GlyR chloride channel. In addition, the  $\beta$  subunit is essential for targeting the receptor to the synapse.

The pharmacology of the GlyR has been studied by different approaches. Besides glycine, the endogenous inhibitory amino acids  $\beta$ -alanine and taurine, as well as  $\beta$ -aminobutyric acid, act as full or partial agonists at the GlyR. Their relative potencies, however, differ between GlyR isoforms. Agonist activation of the GlyR is enhanced by neurosteroids and zinc ions. These ligands are thought to be important for modulating the efficacy of glycinergic synapses *in vivo*. In addition, tropeines, ethanol and anesthetics such as isoflurane and propofol potentiate glycine currents. These compounds constitute the major documented allosteric effectors of the GlyR.

The number of selective GlyR antagonists is still small. Strychnine constitutes the only high-affinity ligand suitable for GlyR binding studies. In addition, the steroid derivative RU5135,  $\omega$ -phosphono- $\alpha$ -amino acid (PMBA) and 5,7-dichloro-4-hydroxyquinoline-3-carboxylic acid (an analog of the NMDA receptor glycine site antagonist 5,7-dichlorokynurenate) antagonize glycine responses of cultured neurons and recombinant GlyRs. Cyanotriphenylborate, a negatively charged structural analog of the cation triphenylmethylphosphonium, has been shown to selectively antagonize GlyR  $\alpha 2$  channels. All homo-oligomeric  $\alpha$  subunit GlyRs are blocked by picrotoxinin.

Mutations in the GlyR  $\alpha 1$  and  $\beta$  subunit genes underlie human startle disease (or hyperekplexia), a rare hereditary neuromotor disorder characterized by exaggerated startle responses to visual or acoustic stimuli. Severe forms cause prolonged myoclonic episodes which, in infants ("stiff baby syndrome"), may even be lethal due to sudden apnea.

# Glycine Receptor

<b>CURRENTLY ACCEPTED NAME</b>	Glycine receptor
<b>ALTERNATIVE NAMES</b>	Strychnine-sensitive glycine receptor, inhibitory glycine receptor
<b>RECEPTOR SELECTIVE AGONISTS</b>	Glycine ( <b>G7126</b> ), $\beta$ -Alanine ( <b>A7752</b> ), Taurine ( <b>T0625</b> )
<b>RECEPTOR SELECTIVE ANTAGONISTS</b>	Strychnine ( <b>S8753</b> ), PMBA ( <b>P204</b> ), Cyanotriphenylborate, 5,7-Dichloro-4-hydroxyquinoline-3-carboxylic acid
<b>POSITIVE MODULATORS</b>	Neurosteroids, Tropeines, Volatile anesthetics (isoflurane, halothane ( <b>H169</b> )), Propofol, Ethanol ( <b>E7023</b> ), Zn <sup>2+</sup>
<b>PERMEATION</b>	Cl <sup>-</sup> (HCO <sub>3</sub> <sup>-</sup> )
<b>RADIOLIGAND OF CHOICE</b>	[ <sup>3</sup> H]-Strychnine
<b>TISSUE EXPRESSION</b>	Central nervous system (spinal cord, brain stem, cerebellum, hippocampus, retina)
<b>PHYSIOLOGICAL FUNCTION</b>	Synaptic inhibition
<b>DISEASE RELEVANCE</b>	Startle disease (hyperekplexia)

## Abbreviations

**PMBA:** Phenylbenzene  $\omega$ -phosphono- $\alpha$ -amino acid

## FOOTNOTES